

HBM and OA: We found that HBM cases had a higher prevalence of hip and knee joint replacement as compared with unaffected family controls. On analysing hip and knee radiographs, compared to a combination of family and population based controls, HBM was associated with an increased risk of osteophytes, but not joint space narrowing. Although HBM cases have an increased risk of obesity, these radiographic associations persisted after BMI adjustment. In further analyses we found that BMD and osteophytes are positively associated with the presence of radiographic enthesophytes, suggesting a more generalised tendency towards bone formation ('bone forming triad'). Taken together, these findings suggest that higher BMD has a causal role in hypertrophic forms of OA, as part of a bony phenotype characterised by a generalised increase in bone formation. As supported by other evidence which suggests that osteophytes directly contribute to pain in OA, there may be a case for developing specific therapeutic strategies for hypertrophic OA.

Targeting the bone phenotype in OA: (i) Biomechanical inputs: Since osteophytes develop in response to disordered biomechanical inputs, hypertrophic OA may preferentially respond to biomechanical interventions such as foot orthoses and muscle strengthening exercises.

(ii) Osteophyte growth: It may be possible to develop drug therapies which target growth of osteophytes (which arise from the periosteum and are produced via a process of endochondral bone formation), without influencing bone remodelling and affecting the risk of osteoporosis. Such an action might explain the beneficial effect of hormone replacement therapy in OA, given oestrogen suppresses aspects of endochondral bone formation and selectively inhibits bone formation at the periosteal surface.

(iii) Nociceptive pathways: Inhibition of inflammatory mediators arising from cartilage, which are thought to contribute to the pathogenesis of pain in OA, may be of little value in treating hypertrophic forms of the disease. However, unlike articular cartilage, subchondral bone and osteophytes are both innervated. Therefore, hypertrophic OA may be helped by inhibition of neuronal nociceptive pathways, for which a range of novel inhibitors are in development, intended to target peripheral pain fibres, spinal cord gate control at the level of the dorsal root ganglion and/or central pain processing.

Conclusion: Further insights into the molecular processes which regulate osteophyte development and osteophytic nociception may be helpful in guiding the development of novel treatments for OA which act by targeting the bony phenotype.

I-19 GENETIC LINKS BETWEEN DEVELOPMENT AND OSTEOARTHRITIS: DIO2 GENE AND RISK FOR OSTEOARTHRITIS

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Previously, in the Genetics osteoArthritis and Progression (GARP) study the deiodinase iodothyronine type II (D2) gene (DIO2) was identified as an OA susceptibility gene with this finding confirmed in other studies especially, for hip OA in females. D2 is critical in maintaining the availability of intracellular active thyroid hormone 3,3',5'-triiodothyronine (T3). In the growth plate, T3 initiates the terminal differentiation of hypertrophic chondrocytes, which is important for the subsequent formation of long bones. Notably, in end-stage versus non-OA cartilage, DIO2 expression was found to be highly upregulated whereas an allelic imbalance was shown for the rs225014 SNP; the mRNA with the OA risk allele 'C' was 30% more abundantly present in articular joint tissues than the wild-type allele 'T'. It was then shown that loss of epigenetic silencing of DIO2 with the OA pathology resulted in a more vivid up regulation of DIO2 particularly in carriers of this risk allele C. Given the function of T3 in the growth plate during development, such signalling in adult articular cartilage is likely detrimental. In this respect, further studies showed that cartilage specific induction of DIO2 expression in adult mice resulted in, OA characteristic, hypertrophic differentiation. Subsequently, in a human in vitro 3D chondrogenesis model of human bone-marrow derived mesenchymal stem cells it was shown that up-regulation of DIO2 expression resulted in a marked reduction in the capacity of chondrocytes to deposit ECM components, concurrent with induction of OA-specific markers of cartilage matrix degeneration and mineralization. In contrast, inhibition of deiodinases contributed to prolonged 'healthy' cartilage homeostasis by virtue of a denser cartilage matrix structure with significant less cellular lacunae. In line with these findings, it was very recent shown that DIO2 knockout mice, have normal articular cartilage development yet, when subjected to a

stringent running regime, appear to be protected against cartilage damage and had reduced severity of synovitis as compared to their wild type littermates. Together these studies show that loss of epigenetic control of the DIO2 gene with ongoing OA pathology affects the propensity of OA chondrocytes recuperate a growth plate morphology and exhibit debilitating expression. Furthermore, focused functional follow-up of OA susceptibility genes to elucidate underlying pathophysiological mechanisms may contribute to a desirable translation from genetic studies towards novel therapeutic options.

I-20 SHOULD OA RESEARCH FOCUS ON "MICE" OR "MEN"?

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Purpose: To argue that osteoarthritis (OA) research should focus on "mice".

Methods: Review the evidence that real and sustainable advances in management and treatment of OA in "men" will ultimately come from "mice", i.e. preclinical research.

Results: The current model for the discovery, development and translation of successful therapies for OA into clinical practice has clearly not been successful. The easy conclusion to draw would be that what works in "mice" is not relevant to "men", and to set aside our preclinical research efforts. In this presentation we will explore in more depth the reasons for translational failure in OA, and make the case that far from cutting preclinical research, we should increase our focus in this area.

Conclusions: Preclinical "mice" research will provide the foundation on which rational and effective OA treatments in "men" will be based.

I-21 SHOULD OA RESEARCH FOCUS ON "MICE" OR "MEN"?

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Purpose: To argue that osteoarthritis research should focus on "men".

Methods: Provide supportive evidence to support the case that osteoarthritis research should focus on human disease. The presentation will also respond to the arguments made that osteoarthritis research should focus on mice.

Results: Given the burden of disease in humans and the limited source of research funding prioritization is required. A case will be made that too much emphasis is placed on research into mice and insufficient focus is made on human research.

Conclusions: There is insufficient focus on human research into osteoarthritis and too great an emphasis is placed on research on mice.

I-22 OSTEOARTHRITIS: INSIGHTS INTO DISEASE INITIATION AND PROGRESSION FROM MR IMAGING

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Purpose: Magnetic Resonance Imaging (MRI) has provided researchers with an opportunity to examine joints non-invasively. Both the morphology and composition of articular cartilage and other tissues can be measured using MRI. A variety of MRI contrast mechanisms exist that can give unique information about tissue composition. This information can gain insight into disease initiation and progression.

Methods: Many different contrast mechanisms are useful with MRI to examine joint morphology. In general, three-dimensional approaches are superior for quantitative evaluation of cartilage volume and thickness. Three-dimensional spoiled gradient echo (SPGR, FLASH) with dark synovial fluid have been used extensively in multiple studies. Other methods with bright synovial fluid include balanced steady state free precession (bSSFP), dual-angle steady state (DESS) MRI, and vastly interpolate projection reconstruction (VIPR). Three-dimensional fast-spin-echo (3D-FSE) is a new method that may enable cartilage morphology and semi-quantitative scoring of other structures with a single acquisition. Important in all of these cartilage studies are accurate image segmentation and registration.

For imaging tissue composition, multiple approaches have proven useful. The collagen matrix of the cartilage and the meniscus can be evaluated with T2 relaxation time mapping, magnetization transfer, and